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This paper discusses the effect that various dialkyl substitutents on chiral pyridino-18-crown-6 ligands have on the molecular recognition of these ligands for the (*R*) and (*S*)-[α-(1-naphthyl)ethyl]ammonium perchlorate. We have systematically synthesized the necessary chiral pyridino-18-crown-6 macrocycles and determined the extent of molecular recognition by titration calorimetry. This paper also discusses possible mechanisms of recognition.

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The Effect of Alkyl Substituents on the Macrocycle Ring on Enantiomeric Recognition by Chiral Pyridino-18-Crown-6 for 1-Naphthylethylamine

by

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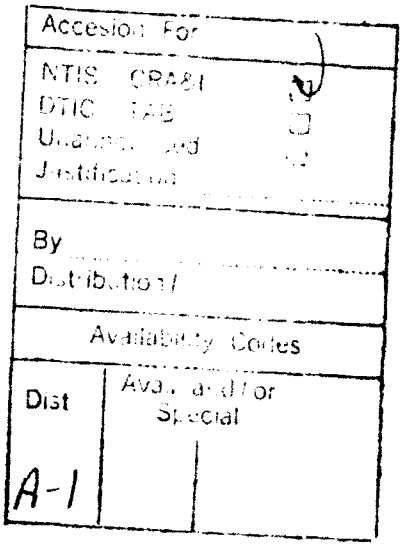


This paper discusses the effect that various dialkyl substitutents on chiral pyridino-18-crown-6 (Py18C6) ligands have on the molecular recognition of these ligands for the (*R*) and (*S*) enantiomers of NapEt. We have systematically synthesized the necessary chiral pyridino-18-crown-6 macrocycles and determined the extent of molecular recognition between enantiomers of primary ammonium cations. We have published the recognition of dimethyl and di-*t*-butyl pyridino-18-crown-6 with various ammonium salts.[1] The recognition, as measured by the $\Delta \log K$, is greater for the di-*tert*-butyl Py18C6 than for the dimethyl Py18C6, although the log *K* values are less. (Table 1) Both effects are thought to be a result of the steric hinderance provided by the bulky *t*-butyl group. Since the recognition difference was large, the next logical step was to determine if the recognition of several intermediate crowns with dialkyl substituents between methyl and *tert*-butyl follow a logical pattern.

Results and Discussion

The crowns presented in this paper are (4*R*,14*R*)-4,14-Di-*iso*-propyl-3,6,9,12,15-pentoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (*iso*-propyl Py18C6), (4*R*,14*R*)-4,14-Di-*iso*-butyl-3,6,9,12,15-pentoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (*iso*-butyl Py18C6), and (4*R*,14*R*)-4,14-Di-[(*S*)-*sec*-butyl-3,6,9,12,15-pentoxa-21-azabicyclo[15.3.1]heneicosa-1(21),17,19-triene (*sec*-butyl Py18C6). (Figure 1) All of the chiral crowns in this paper exhibit typical hydrogen bonding behavior shown in Figure 2. Since the N-H···N hydrogen bond is stronger than the N-H···O hydrogen bond, the ligand bonding always includes the N on the pyridino ring.[2] Since both isomers of NapEt exhibit the same hydrogen

bonding pattern it seems the recognition would come from more stereospecific interactions.

Pi-pi attraction interaction occurs between the naphthyl group of the amine and the pyridino group of the crown ether. The optimum orientation of the naphthyl group is directly over the pyridino group, which allows the strongest interaction between the aromatic rings. (Figure 3) For each NapEt isomer, there are two possible orientations of the three NapEt substituents that allow the optimum pi-pi interaction. For (*R*)-NapEt, with (*R*,*R*) chiral crowns, the guest naphthyl group and/or the methyl group is directed, in both orientations, toward the host alkyl group that lies above the plane of the Py18C6. (Figure 4) For (*S*)-NapEt, with (*R*,*R*) chiral crowns, the naphthyl group and/or the hydrogen is directed, in both orientations, toward the alkyl group that lies above the plane of the Py18C6. (Figure 5) Since hydrogen has a smaller van der Waals radius, the steric hinderance of the alkyl group on the Py18C6 discriminates against (*R*)-NapEt more than (*S*)-NapEt. For both NapEt isomers, hydrogen bonding and the pi-pi interactions are strong enough to form a stable complex.[3]

The more the alkyl group can interfere with the binding of the amine, specifically by sterically hindering the pi-pi interactions, the more selectivity the Py18C6 will show toward NapEt. The order of selectivity, based on this hypothesis, should be *iso*-butyl > *sec*-butyl > *iso*-propyl. This assumes that solvation effects, π-π interaction strengths, hydrogen bonding energies, etc. are the same for each isomer of the NapEt-Py18C6 complex. Table 2 shows that the $\Delta \log K$ values for the crown ethers follow the predicted order. The *iso*-butyl Py18C6 has two methyl "fingers" extending from a two carbon "arm". (Figure 1) These two methyl groups are better able to sterically hinder the binding of the (*R*)-NapEt isomer through random thermal

motion than the *iso*-propyl and *sec*-butyl Py18C6. For *iso*-butyl Py18C6 [(*R*,*R*)-3], the difference in the ΔS value for the NapEt isomers provides most of the recognition. (Figures 6 and 7) The ability of the host alkyl group to move freely even after (*S*)-NapEt is bound increases the ΔS value. When (*R*)-NapEt is bound the movement of the host alkyl group is hindered by the guest naphthyl group. The host alkyl group can come within van der Waals distance of the guest naphthyl group.[4] This restriction of rotation is consistent with a decrease of the ΔS value, thus decreasing the log *K* value. The *sec*-butyl Py18C6 [(*R*,*R*)-2], in comparison, has an ethyl "finger" and a methyl "finger" extending from a one carbon "arm". (Figure 1) Although the ethyl finger on the *sec*-butyl crown extends as far as the *iso*-butyl crown's methyl fingers, there is only one. Again, the difference in ΔS values for the NapEt isomers provides most of the recognition. The selectivity of these Py18C6 compounds is determined by the steric hinderance caused by the host alkyl group as measured by the ΔS values. Based on this logic, it may seem that the *tert*-butyl Py18C6 should have less recognition than the *iso*-butyl Py18C6 or the *sec*-butyl Py18C6 because of the shorter length of the *tert*-butyl group. However, the *tert*-butyl Py18C6 [(*S*,*S*)-5] does not have any hydrogen "fingers" attached to its one carbon "arm". (Figure 1) The tert-butyl Py18C6 may not extend as far, but will always hinder the binding with at least one methyl "finger" at any orientation.

We expected the $\Delta\Delta$log *K* value to be greater when comparing the *sec*- and *iso*-butyl Py18C6. (Figure 8) The *iso*-butyl Py18C6 [(*R*,*R*)-3] should be able to hinder more since it is bulkier at the end of the chain. However, the *iso*-butyl Py18C6 has two hydrogen "fingers" on the first carbon off the crown, so the steric hinderance is more like the dimethyl Py18C6. The NapEt is able to bind closer, thus displacing more solvent from the Py18C6. This explains the slightly larger difference in ΔH values for the *iso*-butyl Py18C6 than for the

sec-butyl Py18C6. The *sec*-butyl Py18C6 [(*R*,*R*)-2] looks more like the *tert*-butyl Py18C6 because it only has one hydrogen "finger" on its first carbon. Thus, it cannot bind as close and displace the solvent, so the ΔH values for the (*R*) and (*S*) isomers are similar. This steric effect accounts for the similar $\Delta \log K$ values.

The *iso*-propyl Py18C6 [(*R*,*R*)-1] has two methyl "fingers" extending from a one carbon "arm". The binding of the amine to this crown is governed by ΔH instead of ΔS. The ΔS value for the binding of the (*S*)-NapEt isomer is actually negative. However, the ΔH value is negative enough to overcome this decrease in entropy. Dimethyl Py18C6 is also enthalpy driven. NapEt is probably able to bind closer to these less bulky Py18C6 hosts, thereby removing solvent molecules which is consistent with the decreased ΔS and ΔH values.

1. Huszthy, P.; Bradshaw, J.S.; Zhu, C.Y.; Izatt, R.M.; Lifson, S. *J. Org. Chem.*, 1991, *56*, 3330-3336.

2. Vinogradov, S.N.; Linnell, K.H. *Hydrogen Bonding*; Van Nostrand Reinhold Co.: New York, 1971.

3. (a) Huszthy, P.; Bradshaw, J.S.; Zhu, C.Y.; Izatt, R.M.; Lifson, S. *J. Org. Chem.*, 1991, *56*, 3330-3336. (b) Zhu, C.Y.; Izatt, R.M.; Bradshaw, J.S.; Dalley, N.K. *J. Incl. Phenom.*, 1992, *13*, 17-27. (c) Izatt, R.M.; Zhu, C.Y.; Bradshaw, J.S. Enantiomeric Recognition in Macrocycle-Primary Ammonium Cation Systems. In *Crown Compounds: Toward Future Applications*; Cooper, S.R., Ed.; VCH: New York, in press.

4. Huszthy, P.; Bradshaw, J.S.; Zhu, C.Y.; Izatt, R.M.; Lifson, S. *J. Org. Chem.*, 1991, *56*, 3330-3336.

Table 1

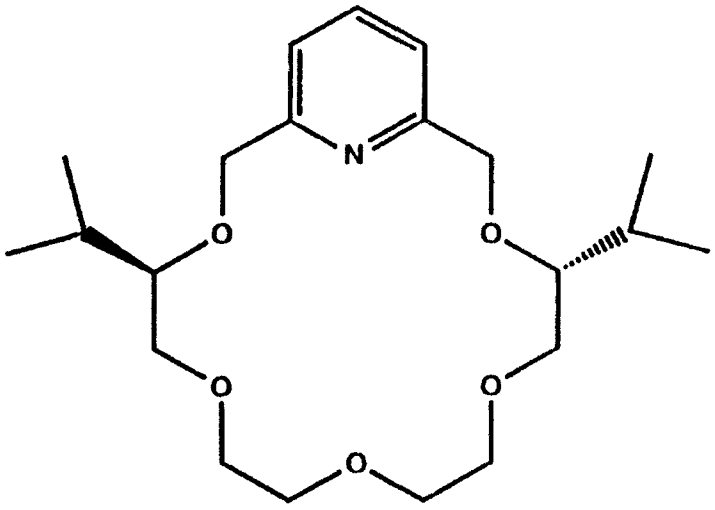
Log *K*, ΔH, ΔS, and Δlog *K* values for the interactions of chiral crown ethers with chiral α-(1-naphthyl)ethylamine (NapEt) in methanol at 25°C.

ligand	Isomer	Log *K*	ΔH(kJ/mol)	TΔS(kJ/mol)
(*S*,*S*)-4	*R*	3.00±0.02	-29.1±0.1	-12.0
	S	2.76±0.02	-22.3±0.1	-6.50
		ΔLog *K* = 0.24		
(*R*,*R*)-5	*R*	1.33±0.05	Data were obtained by NMR so no additional thermodynamic data are available.	
	S	0.62±0.08		
		ΔLog *K* = 0.71		

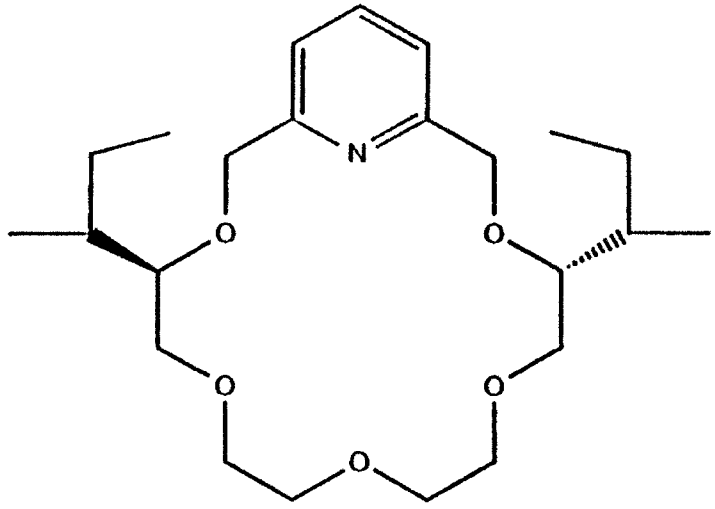
Table 2

Log *K*, ΔH, ΔS, and Δlog *K* values for the interactions of chiral crown ethers with chiral α-(1-naphthyl)ethylamine (NapEt) in methanol at 25°C.

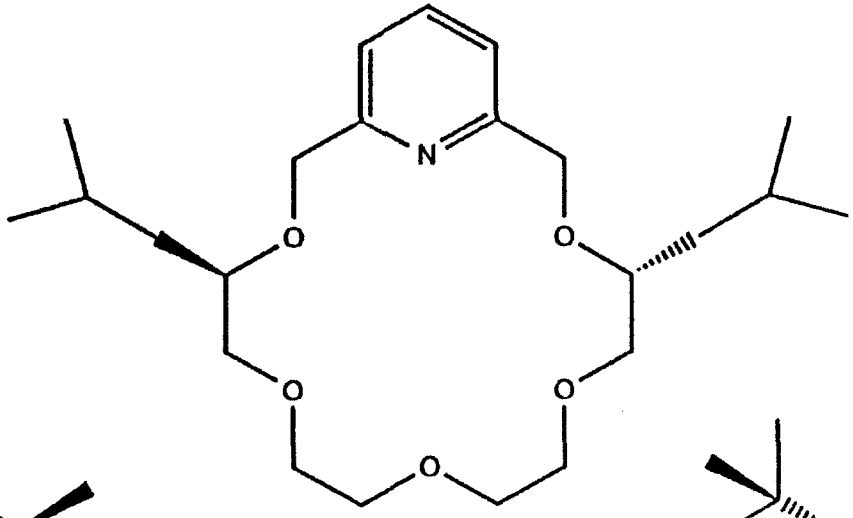
ligand	Isomer	Log *K*	ΔH(kJ/mol)	TΔS(kJ/mol)
(*R*,*R*)-1	*R*	2.18±0.03	-7.8±0.6	4.6
	S	2.36±0.06	-18.8±2.2	-5.4
		ΔLog *K* = 0.18		
(*R*,*R*)-2	*R*	2.05±0.03	-7.2±0.6	4.5
	S	2.47±0.07	-7.5±0.8	6.6
		ΔLog *K* = 0.42		
(*R*,*R*)-3	*R*	2.22±0.03	-9.3±0.6	3.3
	S	2.73±0.05	-10.0±0.7	5.6
		ΔLog *K* = 0.51		



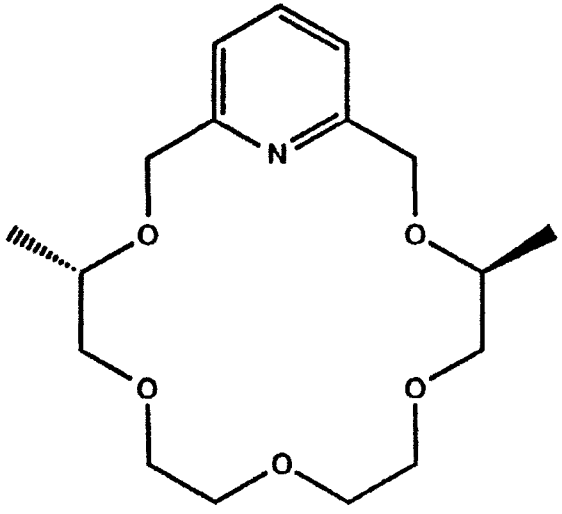
(*R*,*R*)-1 *iso*-propyl Py18C6



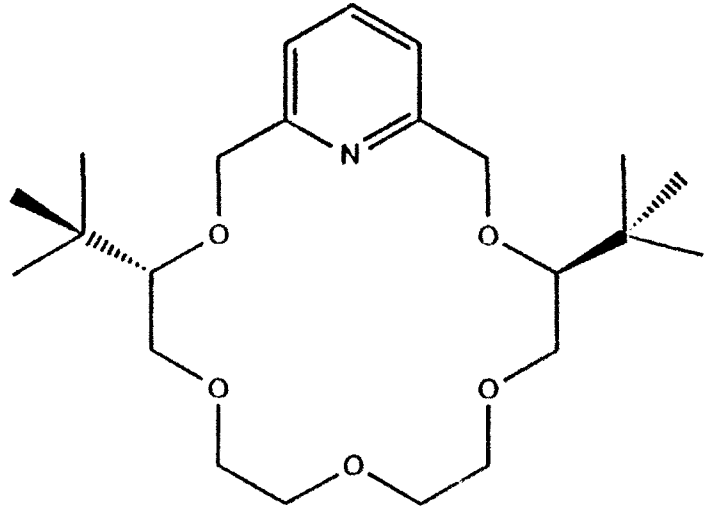
(*R*,*R*)-2 *sec*-butyl Py18C6



(*R*,*R*)-3 *iso*-butyl Py18C6



(*S*,*S*)-4 dimethyl Py18C6



(*S*,*S*)-5 di-*tert*-butyl Py18C6

FIGURE 1

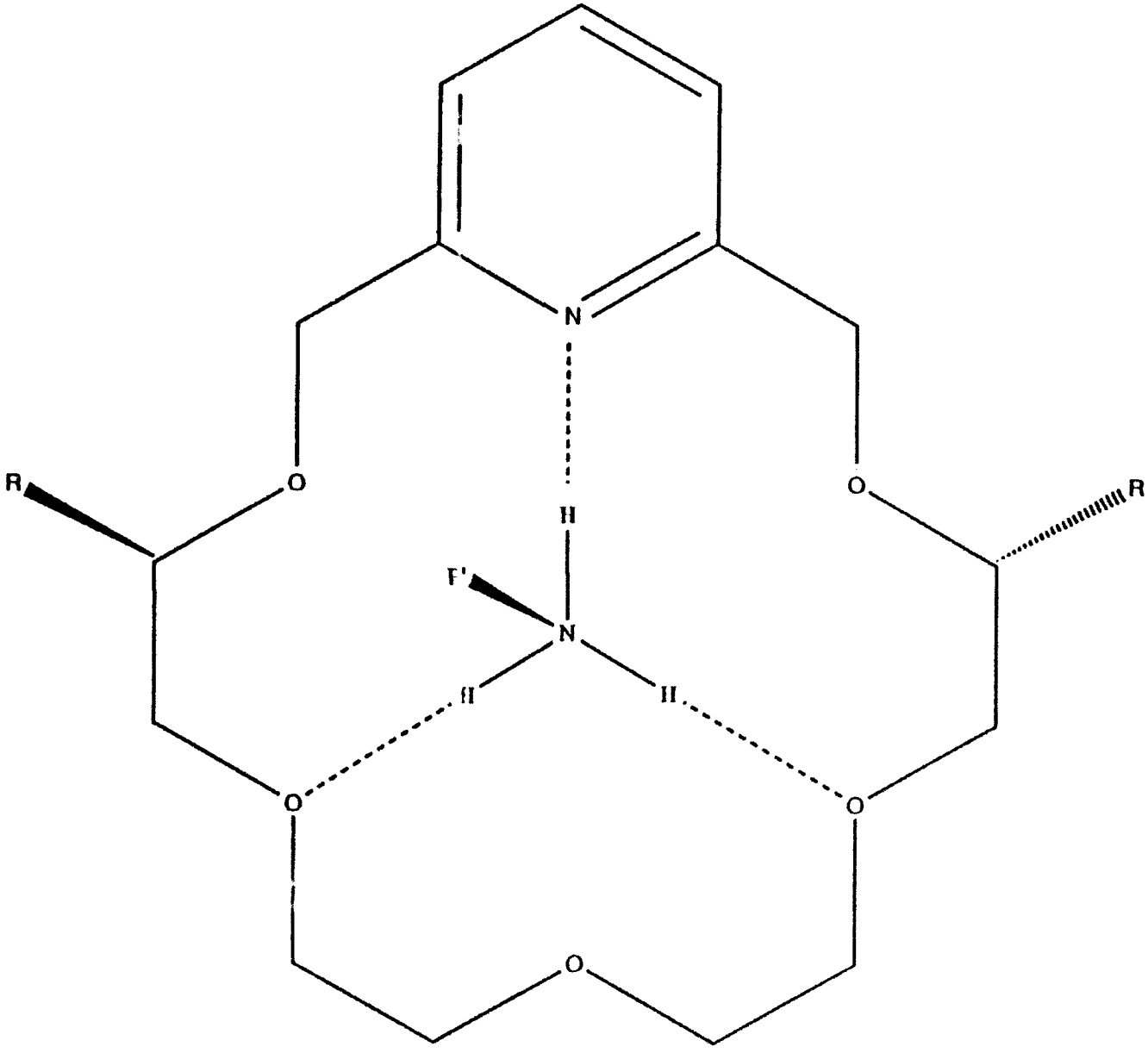


FIGURE 2

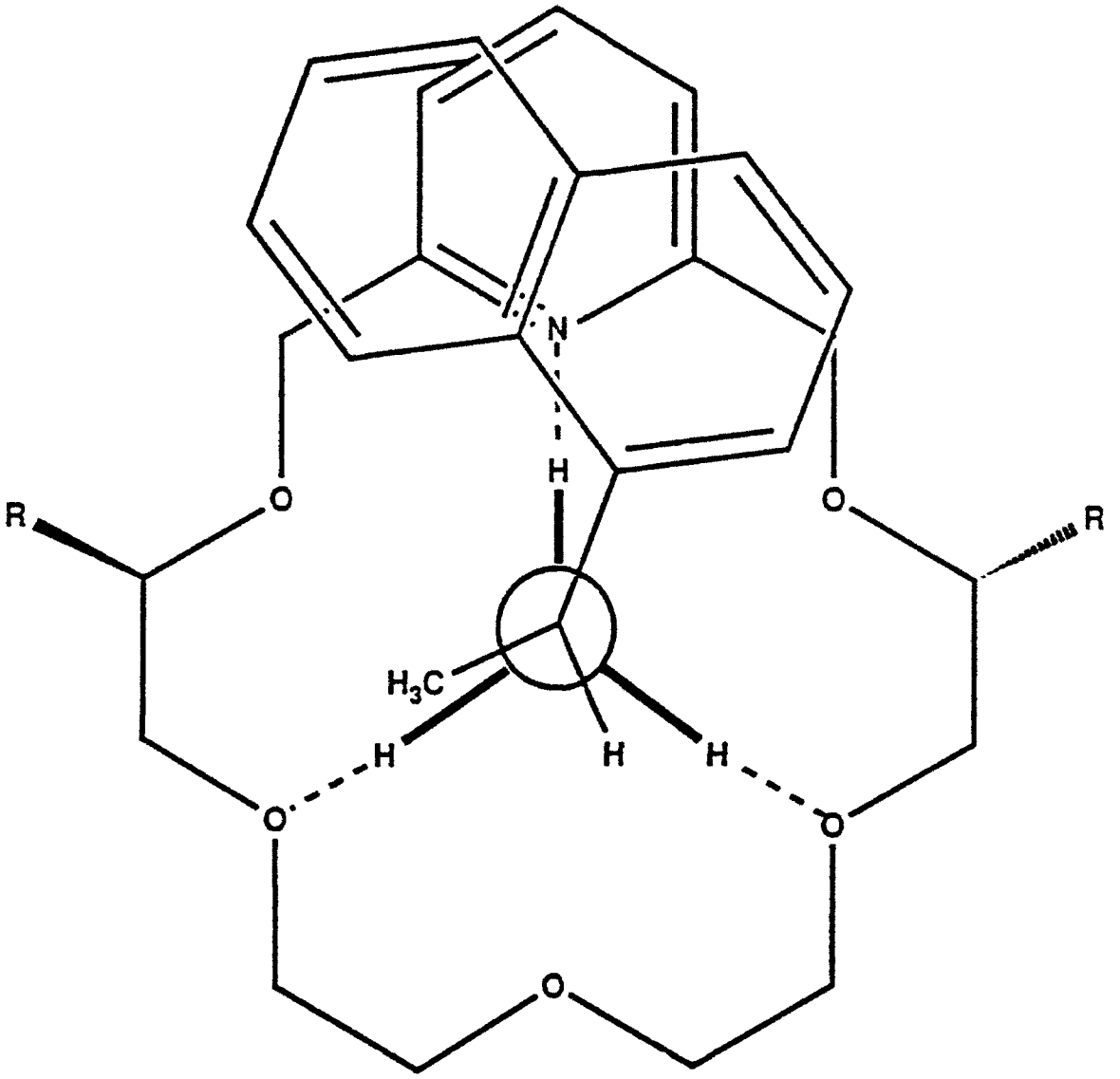
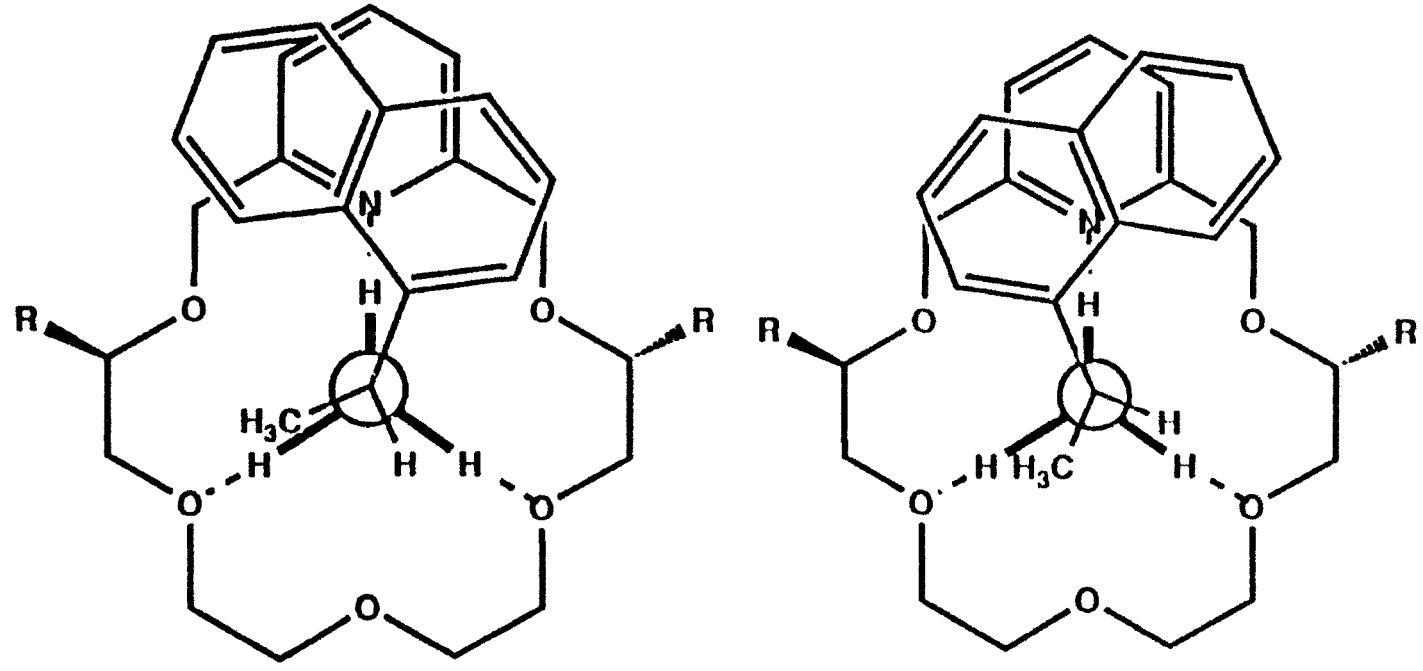
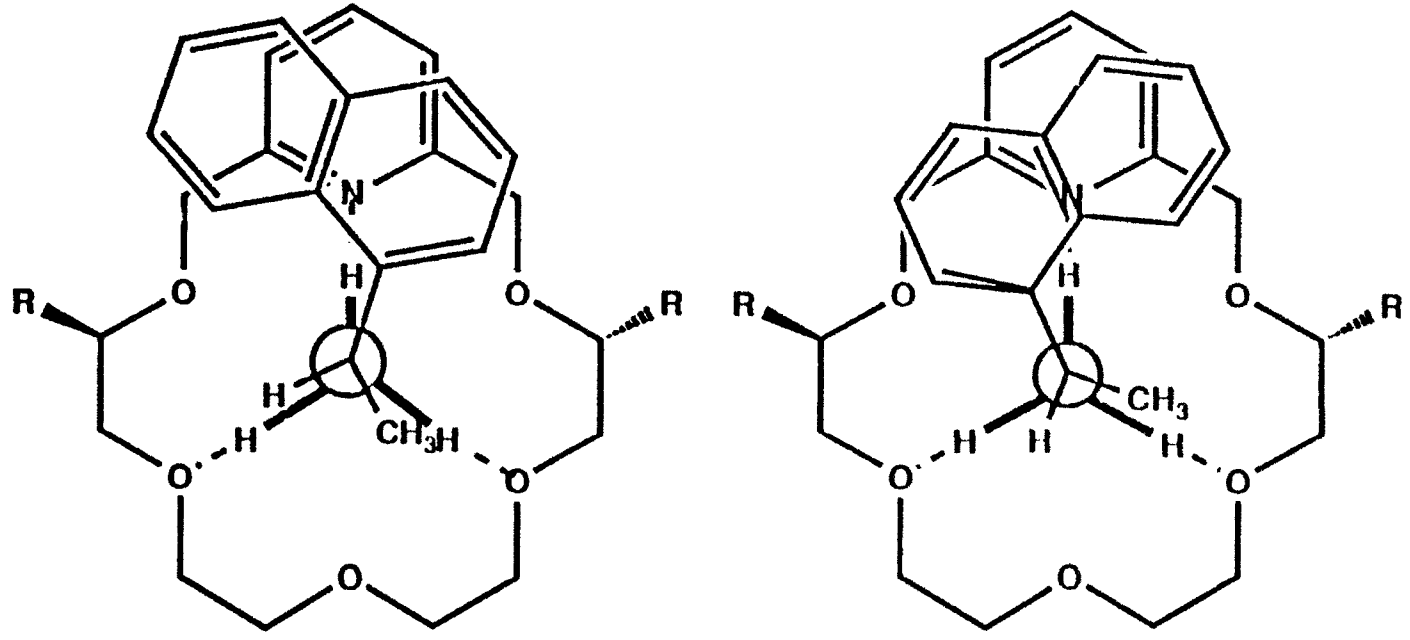


FIGURE 3



(*R*,*R*)-disubstituted pyridino-18-crown-6 with (*R*)-NapEt

FIGURE 4



(*R*,*R*)-disubstituted pyridino-18-crown-6 with (*S*)-NapEt

FIGURE 5

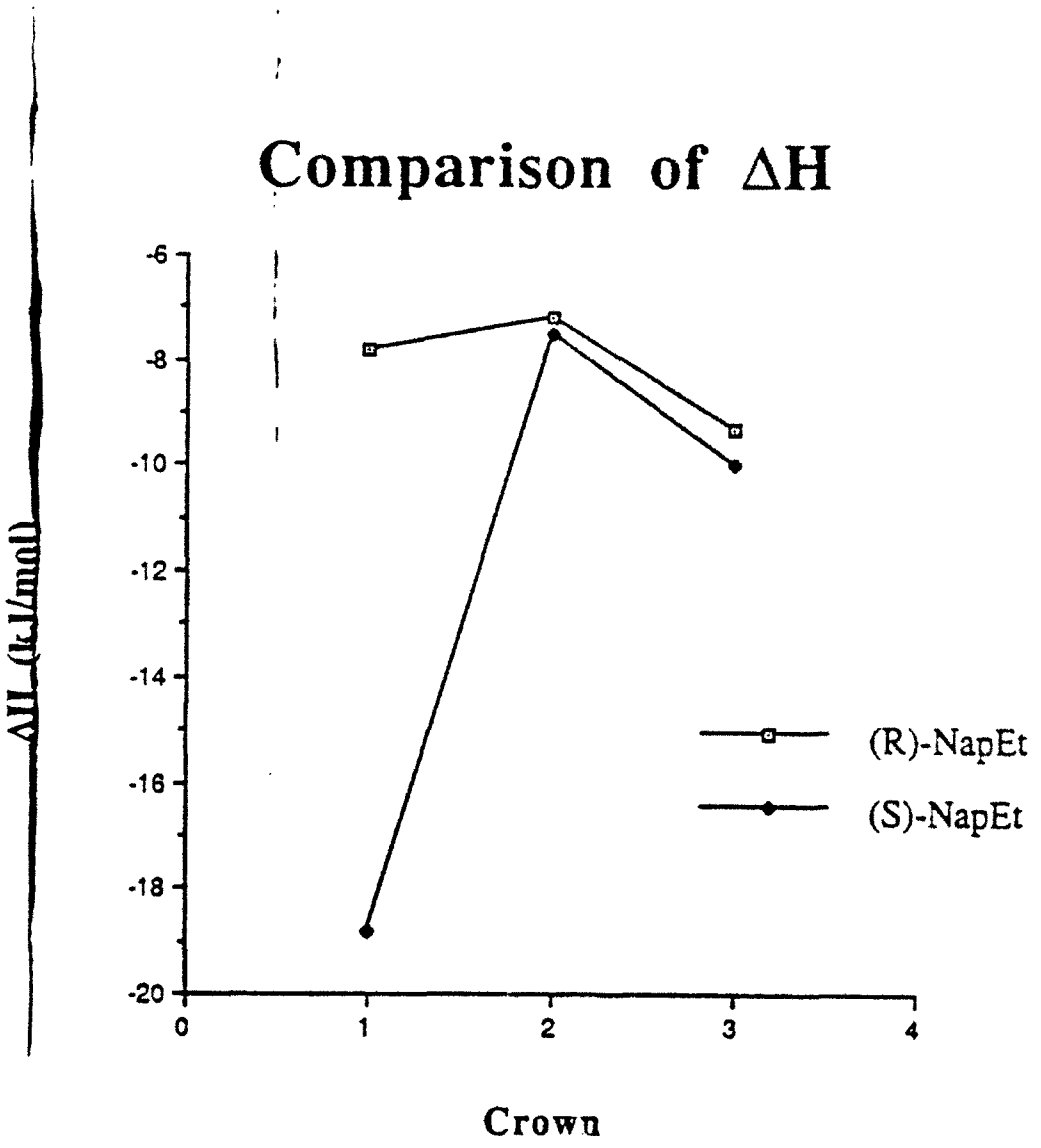

Comparison of ΔH
ΔH (kJ/mol)
-6
-8
-10
-12
-14
-16
-18
-20
0
1
2
3
4
(R)-NapEt
(S)-NapEt
Crown

FIGURE 6

Comparison of TΔS

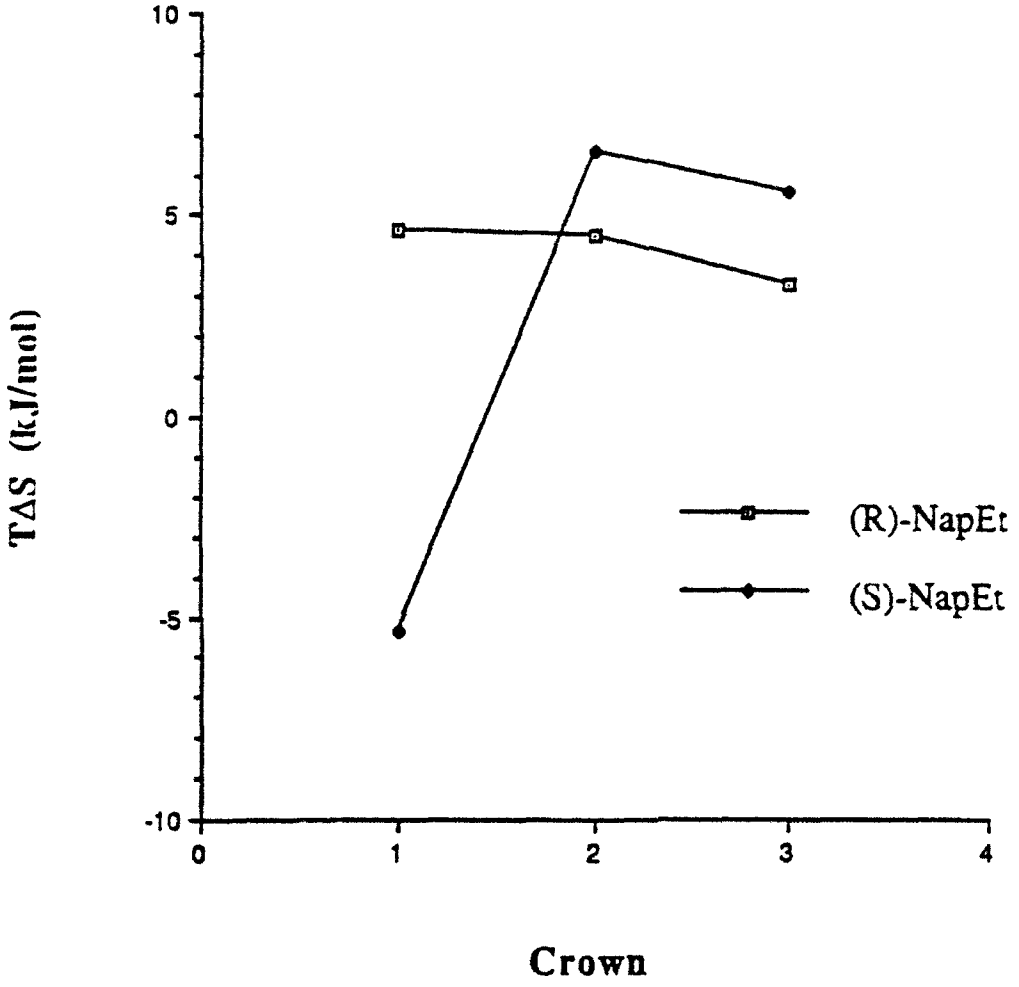


FIGURE 7

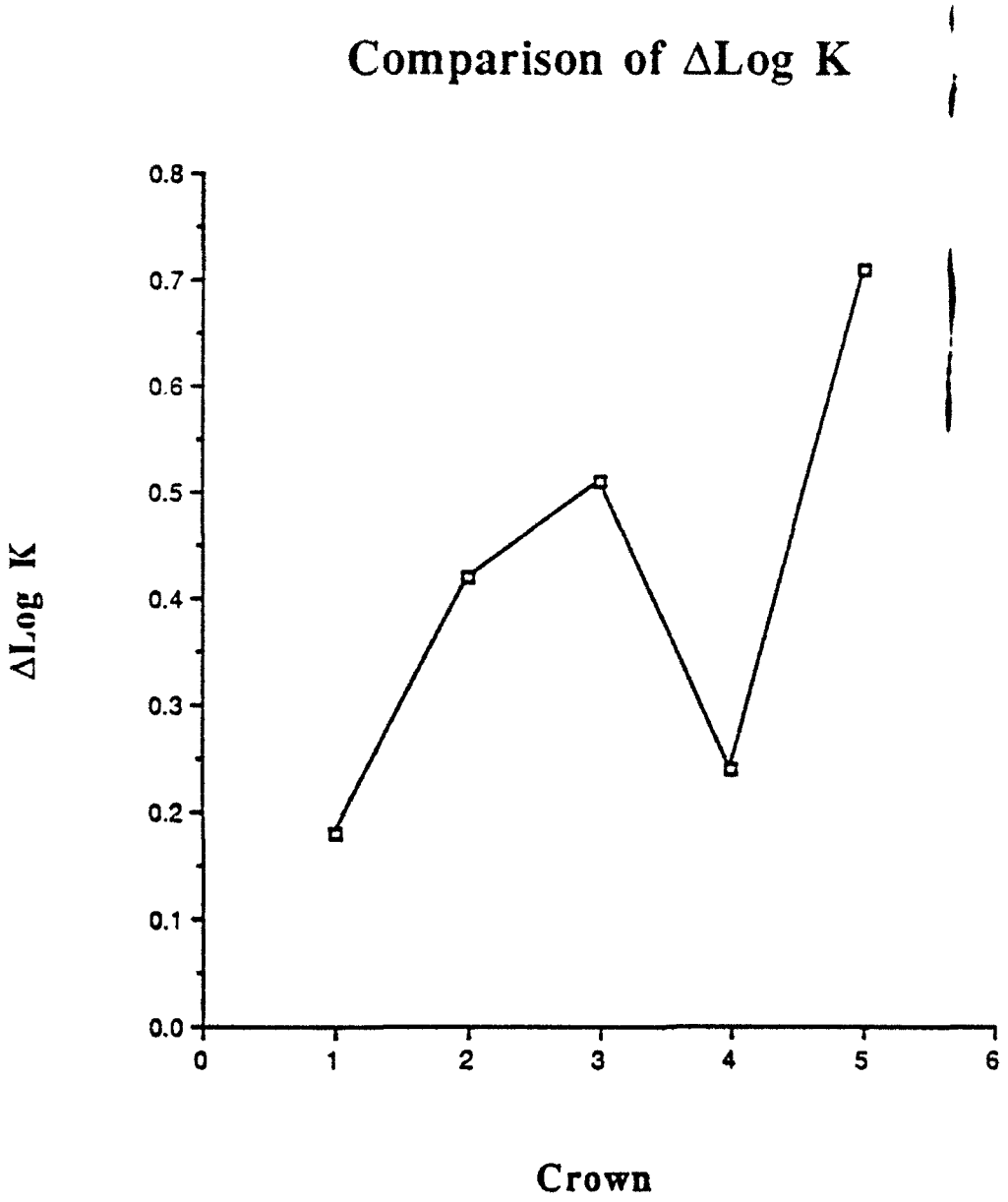

Comparison of ΔLog K
ΔLog K
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
1
2
3
4
5
6
Crown

FIGURE 8